High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools

Ernstoff, Alexi S; Fantke, Peter; Huang, Lei; Jolliet, Olivier

Published in:
Food and Chemical Toxicology

Link to article, DOI:
10.1016/j.fct.2017.09.024

Publication date:
2017

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools

Alexi S. Ernstoff[a*1], Peter Fantke[a], Lei Huang[b], Olivier Jolliet[b]

[a] Quantitative Sustainability Assessment Division, Department of Management Engineering, Technical University of Denmark, Bygningstorvet 116, 2800 Kgs. Lyngby, Denmark

[b] Environmental Health Sciences & Risk Science Center, School of Public Health, University of Michigan, Ann Arbor, Michigan, 48109-2029, United States of America

[*]Corresponding author: Email: AlexiErnstoff@gmail.com

Abstract

Specialty software and simplified models are often used to estimate migration of potentially toxic chemicals from packaging into food. Current models, however, are not suitable for emerging applications in decision-support tools, e.g. in Life Cycle Assessment and risk-based screening and prioritization, which require rapid computation of accurate estimates for diverse scenarios. To fulfil this need, we develop an accurate and rapid (high-throughput) model that estimates the fraction of organic chemicals migrating from polymeric packaging materials into foods. Several hundred step-wise simulations optimised the model coefficients to cover a range of user-defined scenarios (e.g. temperature). The developed model, operationalised in a spreadsheet for future dissemination, nearly instantaneously estimates chemical migration, and has improved performance over commonly used model simplifications. When using measured diffusion coefficients the model accurately

[1] Present address: Quantis International, EPFL Innovation Park, Bât. D, 1015 Lausanne, Switzerland Alexi.Ernstoff@Quantis-intl.com

predicted (R^2 = 0.9, standard error (S_e) = 0.5) hundreds of empirical data points for various scenarios. Diffusion coefficient modelling, which determines the speed of chemical transfer from package to food, was a major contributor to uncertainty and dramatically decreased model performance (R^2 = 0.4, S_e = 1). In all, this study provides a rapid migration modelling approach to estimate exposure to chemicals in food packaging for emerging screening and prioritization approaches.

Keywords: risk; life cycle assessment; low-tier; exposure modelling; product intake fraction; food contact materials

1. Introduction

Food contact materials (FCM) are a source of consumer exposure to potentially hazardous chemicals, such as bisphenol A, phthalates and fluorinated compounds (Begley et al. 2005b; Tittlemier et al. 2007; Apelberg et al. 2007; Cao 2010; Geens et al. 2012). In addition, thousands of other chemicals are legally acceptable in FCM and can lead to human exposure (Geueke et al. 2014; FDA 2015a). Concern over consumer risks are bolstered by data gaps in FCM safety assurance as well as recent hazard information generated by *in silico* and *in vitro* high-throughput toxicity and bioactivity screening studies (Biedermann and Grob 2013a; Neltner et al. 2013; Muncke et al. 2014; Price and Chaudhry 2014; Evans et al. 2016; Karmaus et al. 2016). To estimate potential risks posed by chemicals in FCM, hazard and exposure must be quantified. Empirical exposure data, however, are scarce and analytically challenging to obtain (Rudel et al. 2011). Modelling the migration of chemicals from materials into food is therefore critical to fill empirical data gaps and quantify exposure.

Chemicals in food packaging in particular have been a major focus of consumer exposure assessments that build on migration modelling. The *Cumulative Estimated Daily Intake* (CEDI) database of the

United States Food and Drug Administration (FDA 2015a) and the *Flavourings, Additives, and food Contact materials Exposure Tool* (FACET) (Oldring et al. 2014b) of the European Commission's Joint Research Center (JRC) are recent large-scale advances to estimate realistic exposure to chemicals in food packaging, for 1,302 and 6,499 chemicals, respectively (although only 5 chemicals are pre-installed in FACET as of May 2017). In both cases, exposure estimates (expressed in mg/kg/d) are a function of *undisclosed data e.g. based on an annual country-specific market survey.* By fixing exposure estimates based on undisclosed market-wide occurrences of a chemical in package-food combinations combined with a food consumption estimate, CEDI and FACET cannot be used to estimate exposure to chemicals in packaging per unit(s) of product use, such as one packaged food consumed by one person. Comparing different unit(s) of product use or unit(s) of chemical use (e.g. kilogram of chemical used as a plasticizer in many different polymers) is a main application of emerging exposure screening tools such as SHEDS-HT (Isaacs et al. 2014), ECETOC TRA (Delmaar et al. 2013), USEtox (Rosenbaum et al. 2008), and the PiF framework (Fantke et al. 2016). A per-unit assessment structure facilitates comparing products on a per use basis (regardless of total market volume), or comparing extrapolated uses (e.g. to the entire population or a company-specific production volume). Therefore, in order to be coupled or incorporated within emerging assessment tools, a chemical exposure model for food packaging should have the flexibility to assess various units of packages used by consumers. A major research gap remains, as no peer reviewed tool or method exists to facilitate high-throughput, transparent and flexible estimation of exposure to chemicals in food packaging to support applications in screening and prioritization tools.

With millions of product-chemical combinations on the market, screening has emerged as a resourceful approach to prioritize chemicals and/or products that require further scrutiny. High-Throughput Risk-based Screening (HTRS), and environmental Life Cycle Assessment (LCA) are distinct screening and prioritization tools that can consider potential impacts on human health related to chemical exposure. HTRS combines low-tier high-throughput exposure modelling with risk-based indicators, such as high-throughput screening bioassays (Wambaugh et al. 2013; Isaacs et al. 2014; Wetmore et al. 2015; Shin et al. 2015; Karmaus et al. 2016). LCA is an established sustainability assessment framework that combines multiple modelling approaches to screen product systems and their potential impacts on human health, ecosystems, and natural resources (Hauschild 2005; Hellweg and Milà i Canals 2014). Both HTRS and LCA rely on practical, high-throughput models that require limited parameterization and computational capacity. Exposure models can thereby be designed for both tools despite their different applications (Wambaugh et al. 2013; Shin et al. 2015; Huang et al. 2017a).

High-throughput models, compatible with LCA and HTRS, to estimate exposure to chemicals in food packaging are specifically needed to complement fast-paced advances towards sustainability and resource management targets. Concern over chemicals in food packaging is a barrier to the rising interest in circular economy and use of recycled or re-used materials (Biedermann and Grob 2013b; Lee et al. 2014; European Bureau for Conservation and Development 2015; FDA 2015b; Leslie et al. 2016). Furthermore, bio-based packaging designs (Yuan et al. 2016), or designs to reduce food waste (Siracusa et al. 2014), can also influence packaging materials, their contained chemicals, and their environmental impacts. LCA is extensively used to inform decision making regarding more sustainable

food packaging design (Hunt and Franklin 1996; Flanigan et al. 2013). However, LCA methods traditionally only consider *environmental* exposure pathways, and not indoor exposure pathways related to product use, such exposure to chemicals that have migrated from a package into a food. . To address this inconsistency, there are recent modelling efforts to make LCA more comprehensive and include exposure to chemicals in products (Shin et al. 2012; Jolliet et al. 2015a; Fantke et al. 2016; Ernstoff et al. 2016; Csiszar et al. 2016b; Huang et al. 2017a), although LCA-compatible models do not yet exist to estimate exposure through food packaging.

The objective of this study is thereby to develop a high-throughput (HT) modelling approach for estimating migration of chemicals from packaging into food for emerging applications in screening and prioritization tools, such as LCA and HTRS. The main criteria for our HT approach was to design a rapid, accurate, and accessible migration model—meaning nearly instantaneous computation, representative of the average and not the worst-case, and easily applicable to existing exposure assessment frameworks. To maximize future applicability, the HT model should be valid across chemical-package-food scenarios sensitive to packaging type, thickness, the food type and quantity, and the time and temperature of contact between the package and the food. Archetypal scenarios can be defined in an assessment framework to minimize required user inputs. As a first step we focus on organic chemicals in a single layer of polymeric packaging directly contacting food. Our goals are to 1) analyze commonly used migration models to identify needs for high-throughput approaches, 2) develop a new HT approach for predicting migration for chemical-food-packaging scenarios (e.g. characteristics of package and food, and contact time and temperature) defined by users, 3) and test

the developed approach against other models and empirical migration data available from the United States Food and Drug Administration (US FDA).

2. Methods

2.1 Product intake fraction framework

To quantify exposure to chemicals in food packaging in LCA and HTRS, we propose using the product intake fraction metric (PiF - Jolliet et al. 2015a)—defined as the mass of a chemical taken in by all exposed persons versus the mass of chemical in a product after manufacturing. PiF has been applied to several other groups of consumer products and HT approaches (Shin et al. 2015; Jolliet et al. 2015a; Fantke et al. 2016; Csiszar et al. 2016a; Ernstoff et al. 2016). Assuming that the majority of exposure to chemicals within a manufactured food package occurs via migration into food and not through other pathways (e.g. dermal uptake through contact with package or inhalation via releases into indoor air), PiF = $f_c \times f_t$, where f_t is the time-dependent fraction of the initial mass of chemical in the packaging that has *transferred* (i.e. migrated) into food, and f_c is the fraction of food *consumed* (e.g. not wasted). In the case of food packaging, PiF is specific for each chemical in a given package-food scenario, where a scenario is specified by packaging (material type, thickness, and amount) and food (type and amount) characteristics, and the contact duration and temperature (e.g. according to pasteurization and/or storage).

Values for f_c can be estimated through studies quantifying consumer food waste, f_w, where f_c =1- f_w. Various country-specific studies have found consumer-level wastes between 9-45% depending on the food category (Beretta et al. 2013; Buzby et al. 2014). Accounting for food waste could be especially

114 important in assessments of packaging designs that result in different food spoilage rates (Williams
115 and Wikström 2011; Williams et al. 2012). This study will focus on providing methods to estimate the
116 second parameter f_t through mathematical modelling for various chemical- package-food
117 combinations and scenarios, as f_t is not a value that can be typically obtained from prior studies.

118 **2.2 Analysis of migration model behaviour and needs for a high-throughput model**
119 Various migration models exist to estimate migration of a chemical from FCM into food. Models tend
120 to be computationally complex, require empirical input data for parameterization, or only be valid for
121 specific scenarios (Pocas 2008; Piringer and Baner 2008; Pocas et al. 2012). We focused on widely
122 used migration models that have also been empirically validated and require a limited amount of
123 empirically-derived input parameters (Begley et al. 2005a; Piringer and Baner 2008; Oldring et al.
124 2014b, a; Hoekstra et al. 2015; FDA 2016). The most commonly used migration model is derived from
125 a mass-balance equation based on Fick's second law (Crank 1975). Arranging the terms to solve for
126 the fraction of the initial chemical mass $m_{i,0}$ that has migrated from a package into a food after a
127 contact duration of *t* results in

128 $$f_t = \frac{m_{i,t}}{m_{i,o}} = \left(\frac{\alpha}{1+\alpha}\right)\left[1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(-D_p t_d \frac{q_n^2}{d_p^2}\right)\right] \quad (1)$$

129 where

130 $$\alpha = \frac{1}{K_{P,F}} \frac{V_F}{V_P}.$$

131 Migration of chemical *i* is modelled as a function of the partition coefficient $K_{P,F}$ between package and
132 food; the ratio of food to package volumes V_F/V_P ($cm^3\ cm^{-3}$) the diffusion coefficient for a chemical in

a package, D_P ($cm^2 s^{-1}$); the duration of food-package contact, t_d (s); the thickness of the package, d_P (cm); and the infinite solutions of q_n, where q_n are the positive roots of the transcendental equation $\tan(q_n) = -\alpha q_n$.

The complexity of eq (1) requires specialty software or model simplification which can lead to over or underestimation. A common approach is to obtain values of q_n from a look-up table of 6-50 solutions for pre-specified values of α (Crank 1975; Piringer and Baner 2008; Hoekstra et al. 2015). Another common approach is using short-term diffusion-dominated and long-term partitioning-dominated models, respectively eq (2) and eq (3), where

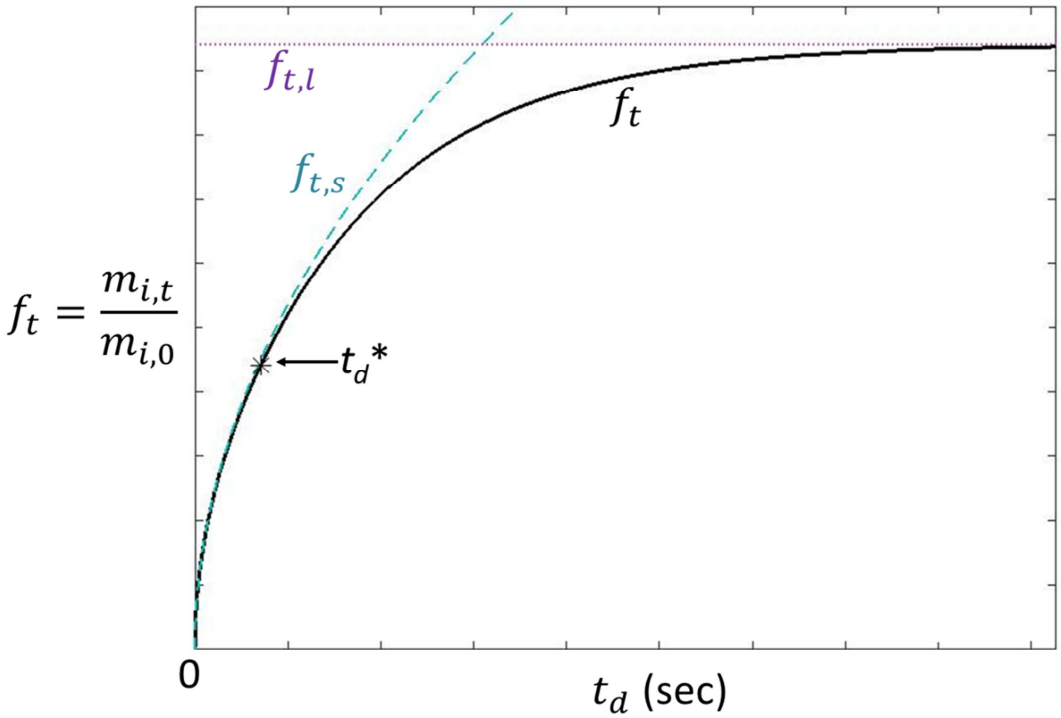
$$f_{t,s} = \frac{m_{i,t}}{m_{i,o}} = 2/d_p \times (D_p t_d/\pi)^{1/2} \quad (2) \text{ and}$$

$$f_{t,l} = \frac{m_{i,t}}{m_{i,o}} = \frac{\alpha}{1+\alpha} \quad (3).$$

The parameters are defined above with eq (1). Eq (2) and (3) are computationally simple, but only valid for restricted timescales, for example eq (3) is valid when $D_p t_d/d_p^2$>>0.001 (Piringer and Baner 2008). To apply eqs (1)-(3), the parameters are either fixed or estimated. For example, regulatory models often fix $K_{P,F}$ = 1 as a claimed "worst-case" scenario, and fix the volume of food to 1000 mL (1 kg) in Europe or 10 g of food in the US. When applying the formulas in regulatory settings, the packaging volume is determined by the typical reference surface area of 6 dm^2 in Europe and 1 in^2 the US, and assuming packaging thickness generally between 0.001-0.1 cm (Oldring et al. 2014b; Hoekstra et al. 2015; FDA 2016). Regardless of the input parameters, eq (2) always surpasses eq (1) at a food-package contact duration referred to in this study as the *deviation time*, t_d*. Using eq (2) beyond t_d*

can result in surpassing the ultimate equilibrium value achieved according to eq (3), and grossly over-estimating migration. Quantification of when t_d* occurs has not been to our knowledge defined, and changes according to the model input parameters.

We programmed simulations in Matlab R2015a to elucidate the behaviour of eq (1) in order to understand the needs for operationalizing HT models. To begin, we investigated the feasibility of using eq (1) and associated simplifications for HT modelling. Specifically, we elucidated the consequences on the model behaviour when simulations of eq (1) were performed a) with a limited number of q_n roots or b) using a fixed value for input parameter $K_{P,F}$. We also compared the behaviour of eq (1) with eq (2) and eq (3). Figure 1 is a generic representation of the model system with a sufficient number of q_n roots to achieve eq (1) with accuracy; the required number of q_n roots as well as the shape of the f_t curve and values on the X and Y axes will differ depending on input parameters.



164

165 Figure 1. Representation of model behaviour through an undefined package-food contact duration.
166 Eqs (1) f_t (solid line) with sufficient q_n roots, (2) $f_{t,s}$ (dashed line), and (3) $f_{t,l}$ (dotted line), are
167 demonstrated. The point at which the short term simplification deviates from the model with >99%
168 accuracy, t_d*, is indicated with a star.

169 Preliminary simulations demonstrated that the number of q_n roots needed to estimate eq (1) with
170 high accuracy (e.g. up to 99%) cannot easily be predetermined; in addition to the relationship
171 $D_p t_d / d_p^2$ (Piringer and Baner 2008), the number of q_n roots required to accurately estimate eq (1) is
172 also dependent on α.We found as α decreases the number of roots required to obtain eq (1) increases
173 (Figure S1A-B). The number of roots and thus iterative calculations affected the required computation
174 time. We found generally when α was high (> 10) computation time was rapid and few roots were

needed (e.g. 5 - 50,000). For very low α (< 0.001) even 1 million roots resulted in several orders of magnitude overestimation during short time scales (i.e. in the first 24 hours). Taking 1 million roots substantially lengthened the computation time. Restricting the number of q_n values to rapidly solve eq (1) always led to overestimation of the model f_t at short time scales (supporting information (SI), Figure S1A-B), typically by several orders of magnitude. This suggests using a limited number of q_n can be appropriate for safety assessments, but does not provide a realistic estimation, especially at short time scales and for low values of α. In all, using eq (1) is not practical for rapid and accessible HT methods that are operational across all time scales and values of α. Iterative calculation steps can lengthen computation time and furthermore poses a computational barrier to pragmatically coupling of the model to spreadsheet-based tools.

The partition coefficient between packaging and food for a migrant, $K_{P,F}$, is an important parameter influencing the behaviour of eq (1) and eq (3). When $K_{P,F}$ is high the chemical has higher affinity for the package, and when $K_{P,F}$ is low (e.g. $K_{P,F} < 1$) the compound has higher affinity for the food (Tehrany and Desobry 2004; Ozaki et al. 2010). When analysing model behaviour to inform method development we found *no evidence* that the simplification of $K_{P,F} = 1$ is a "worst-case" scenario as claimed by regulatory documents and publications (e.g. Brandsch et al. 2002; Begley et al. 2005a; Hoekstra et al. 2015). We found that setting $K_{P,F} < 1$ can lead to migration estimates greater than the model outcome when $K_{P,F} = 1$, especially when the food and packaging volume are of similar magnitude. $K_{P,F} < 1$ have also been observed empirically (Tehrany and Desobry 2004; Piringer and Baner 2008; Ozaki et al. 2010). Quantitatively, $K_{P,F} = 1$ corresponds to the chemical concentration being *equal* in the package and the food. Our simulations demonstrated that setting $K_{P,F} = 1$ can

196 underestimate the migrated chemical mass at equilibrium, e.g. by a factor of ≈2 when $K_{P,F}$ <= 0.1
197 when the volumes of food and packaging material are equivalent (SI Figure S2A versus S2B when $K_{P,F}$ =
198 1), and this factor increases if the ratio between the package and food increases above 1. Therefore,
199 in situations when the mass of packaging material approaches the mass of the food (e.g. for small
200 candies, capsules, and single-serving condiments) and equilibrium can be approached or reached—
201 e.g. due to a long contact time, small package thickness, and/or due to rapid diffusion—$K_{P,F}$ cannot be
202 set to 1 to obtain a realistic *or* worst-case value for chemicals with $K_{P,F} < 1$. Using the default
203 regulatory values for the amounts of packaging and food, the assumption $K_{P,F} = 1$ provides *nearly* an
204 upper-bound (worst-case) estimate of eq (1) (SI Figure S2B). There is substantial empirical evidence
205 that chemicals in polymers can have $K_{P,F} < 1$, and < 0.01, (Mercea 2008), however, we cannot
206 determine the frequency such chemicals occur in situations where packaging and food volumes are
207 similar. Nevertheless, we recommend that regulatory documents and other publications do not state
208 that $K_{P,F} = 1$ is a "worst-case" scenario. Instead, we recommend stating that setting $K_{P,F} = 1$ is a
209 pragmatic approximation of a worst-case scenario when the volume ratio of food to package is >100.
210 Moreover analysing the consequence of setting $K_{P,F} = 1$ points to a need for a model to estimate $K_{P,F}$ to
211 be used in HT estimates of realistic exposure, as setting $K_{P,F} = 1$ can overestimate exposure when $K_{P,F} >$
212 1, and underestimate exposure when $K_{P,F} < 1$.

213 To summarize, analysing the behaviour of existing modelling approaches demonstrated that using
214 too few q_n roots can lead to drastic overestimation of eq (1), but that using more q_n roots slows
215 computation times; eq (2) is a simple and accurate method suitable for HT estimates of migration for
216 short timescales (< t_d*), but this timescale is not well defined; and setting $K_{P,F} = 1$ does not provide

either representative or worst-case estimates for all scenarios. These findings informed the research needs for developing an HT model that can rapidly provide representative migration estimates across all timescales and for a variety of chemical-package-food combinations. Specifically, the identified needs are to 1) design a model that does not require iterative calculations based on q_n roots, 2) identify package-food contact duration, t_d^*, where eq (2) is no longer valid and 3) more accurately estimate $K_{P,F}$.

2.3 Development of a high-throughput model for migration estimation

To address these three needs, we aimed to develop a parsimonious approach valid for all time-scales and a large range of input parameters.

First we defined t_d^* (Figure 1) as the contact duration between package and food when the solution to eq (2) deviates from the solution of eq (1) by more than >1% of the ultimate equilibrium value. At contact durations < t_d^* eq (2) is valid, compares well with eq (1) (R2≈ 1) and thus eq (2) can be directly used for HT approaches in this time range. To determine t_d^* as an explicit function of main parameters, we hypothesized that it is a function of α, D_P, and d_P due to the influence of these parameters on the function behaviour. To test this hypothesis we obtained t_d^* from several hundred simulations for random permutations of the input parameters D_P (10^{-10}, 10^{-20} cm^2/sec), α (values randomly generated between 10^{-6} and 10^{5}), and d_P (0.01, 0.1, 1 cm), using up to 1 million roots in eq (1) to ensure high accuracy. Next, we plotted the resulting values of t_d^* as function of α, D_P, and d_P and used the Matlab 2015a Curve Fitting Toolbox™ to determine an explicit function of these variables and enabling prediction of t_d^* with reasonable accuracy.

After determining a predictive function for t_d*, we aimed to develop an HT migration model valid after t_d*. The model theory is based on recent work by Huang & Jolliet (2016) where a parsimonious model was developed for HT prediction of volatile organic compound releases from solid materials. This approach demonstrated a Fickian-based differential equation requiring the infinite sum of q_n roots, similar to eq (1), can be approximated as a two-term exponential decay model (Huang and Jolliet 2016). The first exponential term captures short-term diffusion-dominated behaviour and the second exponential term captures long-term partitioning-dominated behaviour (Chang and Guo 1992). A model of this form relates the mass transferred (lost from the material) through time, m(t), as a function of the initial mass, m_0, in the material multiplied by an exponential decay with constant k, $m(t) = m_0 e^{-kt}$. When estimating the fraction of chemical mass initially in the material (i.e. the package) that has transferred (i.e. into the food) this results in the form $1- e^{-kt}$. We therefore hypothesized that a 2-term decay model in the form of $1- e^{-kt}$ could capture the behaviour of eq (1). Furthermore, since the shape of eq (1) through time is determined by input parameters α, D_P, and d_P, likewise the exponential shape parameters (analogous to the decay constant) could be predicted as a function of α, D_P, and d_P. We found that one exponential term sufficed (R^2>0.99) when α ≈>10 and there were no partitioning constraints (given infinite time nearly all of the chemical will have transferred from package to food), however, in order to obtain high values of R^2 (R^2>0.97) when comparing the simplification to eq (1) across values of α two exponential terms were needed (SI Figure S3) (eq 4). We therefore followed a two exponential form in order to provide a model valid for all values of α. The resulting model form for all contact durations and values of α was determined as

$$f_{t,p} = \begin{cases} \frac{2}{d_p} \times (D_p\, t_d/\pi)^{\frac{1}{2}} \text{ eq(2)} & \text{if } t_d \le t_d{}^*, \text{ else} \\ y_{t_d} + \left(\frac{\alpha}{1+\alpha} - y_{t_d}\right) \times \left(A \times \left(1 - e^{-B\times\beta\times(t_d - t_d{}^*)}\right) + (1-A) \times \left(1 - e^{-C\times\beta(t_d - t_d{}^*)}\right)\right), \end{cases} \quad (4)$$

$$\text{where } \beta = \frac{D_p N_{t_d{}^*}}{{d_p}^2},$$

and where A, B, and C are varying coefficients discussed further below; slope factor N_{t_d} is the derivative of eq (2) at the contact duration t_d* to train the slope towards the slope of eq (2) at that point; y_{t_d} is the vertical shift to begin the double exponential model at contact duration t_d* and is equal to the value of eq (2) at t_d*; other equation parameters are defined within eq (1).

To operationalize eq (4), coefficients A, B, C, must be determined as explicit function of main parameters. Based on observations from the initial simulations, we hypothesized each coefficient is interdependent and a function of α. To test this hypothesis, we ran simulations of f_t as well as the predicted function $f_{t,p}$ using random permutations of input parameters to cover range of potential migration scenarios, i.e. for D_P (10^{-10}, 10^{-20} cm^2/sec), α (values randomly generated between 10^{-6} and 10^{5}) and d_P (0.01, 0.1, 1 cm) with up to 1 million roots to ensure accuracy. These simulations were used to develop predictive models for the coefficients A, B, and C, applying the following stepwise procedure to iteratively restrict noise due to interactions between these parameters:

The first step was to investigate values of A, B, and C as a function of α as completely "free" variables, optimised by minimizing the residual squares between eq (4) and eq (1) using the Matlab 2015a pre-existing function *fminsearch*. From this exercise we observed that values of A were being optimised to force the equation towards a 1-exponential (e.g. A approaches 1) when α ≈>10. We then fixed A as a

piece-wise function of α and ran simulations to predict values of B and C. Again seeing that B was forced towards 1 at high values of α, we then also fixed B as piece-wise functions of α to finally obtain a predictive function of C.

Finally we tested the accuracy of eq (4) at estimating f_t eq (1) when using the final resulting predictions of t_d, A, B, and C. Because $f_{t,s}$ eq (2) and $f_{t,l}$ eq (3) model short and long-term behaviour, we also compared our modelling approach to a simple approach using $f_{t,s}$ until it is equal to $f_{t,l}$ and then switching to $f_{t,l}$. Nine simulations were run to cover the range of α from (10^{-4}-10^{3}), where the simulation time for low values of α was extensive due to the number of q_n roots required.

2.4 Model parameterization

Chemical diffusion coefficient: Chemical diffusion is influenced by material and chemical properties (e.g. molecular size) as well as the ambient temperature. Diffusion coefficients are commonly estimated using eq (5) (Brandsch 2000; Mercea 2000; Begley et al. 2005a; Hoekstra et al. 2015)

$$D_P = D_o \exp\left(A_P - 0.1351MW^{\frac{2}{3}} + 0.003MW - \frac{10454}{T}\right)\left(\frac{cm^2}{s}\right) \quad (5)$$

where $A_P = A'_P - \frac{\tau}{T}$, $D_o = 1$ m²/s $= 10^4$ cm²/s and $R = 8.3145$ J mol^{-1} K^{-1}.

Molecular weight (MW g/mol) is specific to the migrant; A_P is a dimensionless polymer-specific diffusivity parameter that is sensitive to the ambient temperature, T (K) of the food-material system; τ and the constant 10,454 are polymer-specific and account for the diffusion activation energy (where 10,454 is the reference constant for polyethylene) (Barnes et al. 2006). When applying this model in regulatory settings typically "worst case" values of A_P are used. LCA compatible models do not

typically estimate worst case scenarios but aim to estimate average scenarios, therefore to estimate A_P we used average values (*not 'upper-bound' or worst case*) of $A_P^{'}$ (a standard polymer-specific diffusivity parameter) which we calculated from data listed in Begley et al. 2005a as listed in SI Table S1. The diffusion coefficient is highly sensitive to $\mathrm{A'_P}$ where a 10% change in $\mathrm{A'_P}$ can lead to a 300% change in the diffusion coefficient. The full model, eq (1), however, is less sensitive to changes in the diffusion coefficient (e.g. a 10% change in the diffusion coefficient leads to a <5% change in model output), where the level of sensitivity depends on the contact duration and if this is in the diffusion-dominated timescale.

Package-food partition coefficient: As discussed in Section 2.2 the partition coefficient $K_{P,F}$ influences model behaviour after contact duration t_d* and $K_{P,F}$ cannot be set to a fixed value to obtain realistic estimates. Therefore, we focus on developing HT methods to estimate $K_{P,F}$ for various scenarios. Previous works (Tehrany and Desobry 2005; Tehrany et al. 2006; Ozaki et al. 2010) to this aim have developed correlations of $K_{P,F}$ with the chemical and food lipophilicity, where the octanol-water partition coefficient, K_{ow}, is used as a the chemical proxy and the simulant ethanol-equivalency EtOH-eq is used as the food proxy. $K_{P,F}$ is also temperature sensitive but the relationship is not known to be easily predictable (Tehrany and Desobry 2004). In this study we do not attempt to predict the temperature-dependency of $K_{P,F}$. We build on more recent empirical work by Ozaki et al. 2010 correlating $K_{P,F}$ with a range of chemical log K_{ow}s and across a range of food EtOH-eqs. The FACET project (Seiler et al. 2014) also built on this work and performed experiments to extend the correlation range of $K_{P,F}$, but the experimental data and subsequent correlations are not available to our knowledge.

Therefore, we developed a method to estimate $K_{P,F}$ as a function of a chemical K_{ow} and food EtOH-eq by generalizing the three log-log linear EtOH-eq correlations in Ozaki et al. 2010 to all potential combinations of EtOH-eq and K_{ow}. We assumed the gradient between the slopes of these log-log linear curves would be uniformly distributed across EtOH-eqs and therefore follows the format $\log K_{P,F} = m(\mathrm{EtOH-eq}) \times \log(K_{ow}) - b$, with m a linear function of EtOH-eq. The solver add-in in Microsoft Excel 2010 was used to optimize the parameters of a log-log linear model while minimizing the residual error between our predicted values and the measured values from Ozaki et al. 2010. We restricted the applicability range of the $K_{P,F}$ correlations according to the K_{ow} values empirically

measured in Ozaki et al. 2010, e.g. data were not available for chemicals with log K_{ow} >≈5, 8, 18 when the EtOH-eq is ≈10, 50, 95% respectively. Finally, to test the accuracy of our modelling approach by external validation, we obtained a separate dataset of 163 different experiments that measured partition coefficients between LDPE and HDPE polymers and 13 different foods at ambient temperature 296 K (Mercea 2008). We assigned these 13 different foods to EtOH-eq according to SI Table S2.

2.5 Applying the high-throughput estimation approach – external validation

We ran the developed HT model to predict migration for various chemical, package, and food combinations that have empirical data available. The empirical data were provided by request from the US FDA (FDA 2016). These requested data are used to provide industrial guidance for pre-market submissions, and the data set contains 12,773 independent measurements for migration.

Most of the migration measurements in the database also included the parameters needed for modelling, e.g. according to eq (4), specifically the tested chemical's MW and K_{ow}, the food or simulant tested, the polymer tested and its thickness, the duration and temperature of the test. Entries reporting a "0" starting concentration of a chemical in a polymer, or reporting that the final migrated mass into a simulant or food exceeded the initial mass in the tested material (perhaps due to experimental uncertainty) were disregarded. Diffusion coefficients are also provided for each experiment in the spreadsheet. Several parameters required for modelling were also not reported in the database, for example $A_P^{'}$ which is required to model the diffusion coefficient, and EtOH-eq of the food or simulant which is required to model the partition coefficient. We therefore matched the database to the available polymer-specific average $A_P^{'}$ (Section 2.4.1; SI Table S1) and a list of EtOH-eq

matched to food or simulants (SI Table S2) in order to simulate each applicable experimental value. 4,492 applicable experimental values remained with available $A_P^{'}$, and EtOH-eq. Migration modelling was then performed using three different approaches: A) the HT model (Table 1) and *using measured diffusion coefficients from the database,* B) applying the HT model (Table 1) and using *modelled diffusion coefficients estimated with eq* (5), and finally C) using a combination of eq (2) (diffusion-dominated model) and (3) (partition denominated model) and taking the minimum value, i.e. the value of eq (2) until it intersects with eq (3), and then the value of eq (3). . The two first modelling approaches A and B were employed to elucidate the contribution of the estimated diffusion coefficient to model uncertainty. The final approach C, is the most simple and was tested against the first two approaches A and B.

3. Results and discussion

3.1 Development of an accurate model for high-throughput migration modelling

Model development: The operationalised form of the HT migration model eq (4), including estimates for t_d*, A, B, and C is compiled in Table 1. Predicting t_d* first is important for knowing the contact duration after which the simplified diffusion eq (2) is no longer valid, and also to serve as input for eq (4). To avoid over-estimating t_d*, which would jeopardize the predictive ability of the model, we determined two equations to predict t_d*as a function of α, i.e. one for $\alpha \leq 0.2$ and one for $\alpha > 0.2$ as described by eq (6) in Table 1, with a high accuracy ($R^2 \approx 1$, Figure S4C). The coefficients A, B, and C of the HT migration model are obtained as a direct function of alpha as defined by equation (8a,b,c) of Table 1 and the stepwise procedure to determine these is further detailed in SI Figure S5.

364 t_d* is proportional to the ratio d_P^2/D_P which we have defined as a characteristic time of migration
365 (CTM (s), see SI Figure S4) as a function of the thickness of the diffusive path length and the diffusion
366 coefficient. . CTM can range from a few hours to thousands of years depending on the packaging
367 thickness and diffusion coefficient (Figure 2). t_d* may only be a small fraction of CTM, and the fraction
368 lessens as α and the equilibrium value decrease.

369 Table 1. Final high-throughput estimation model and required parameters.

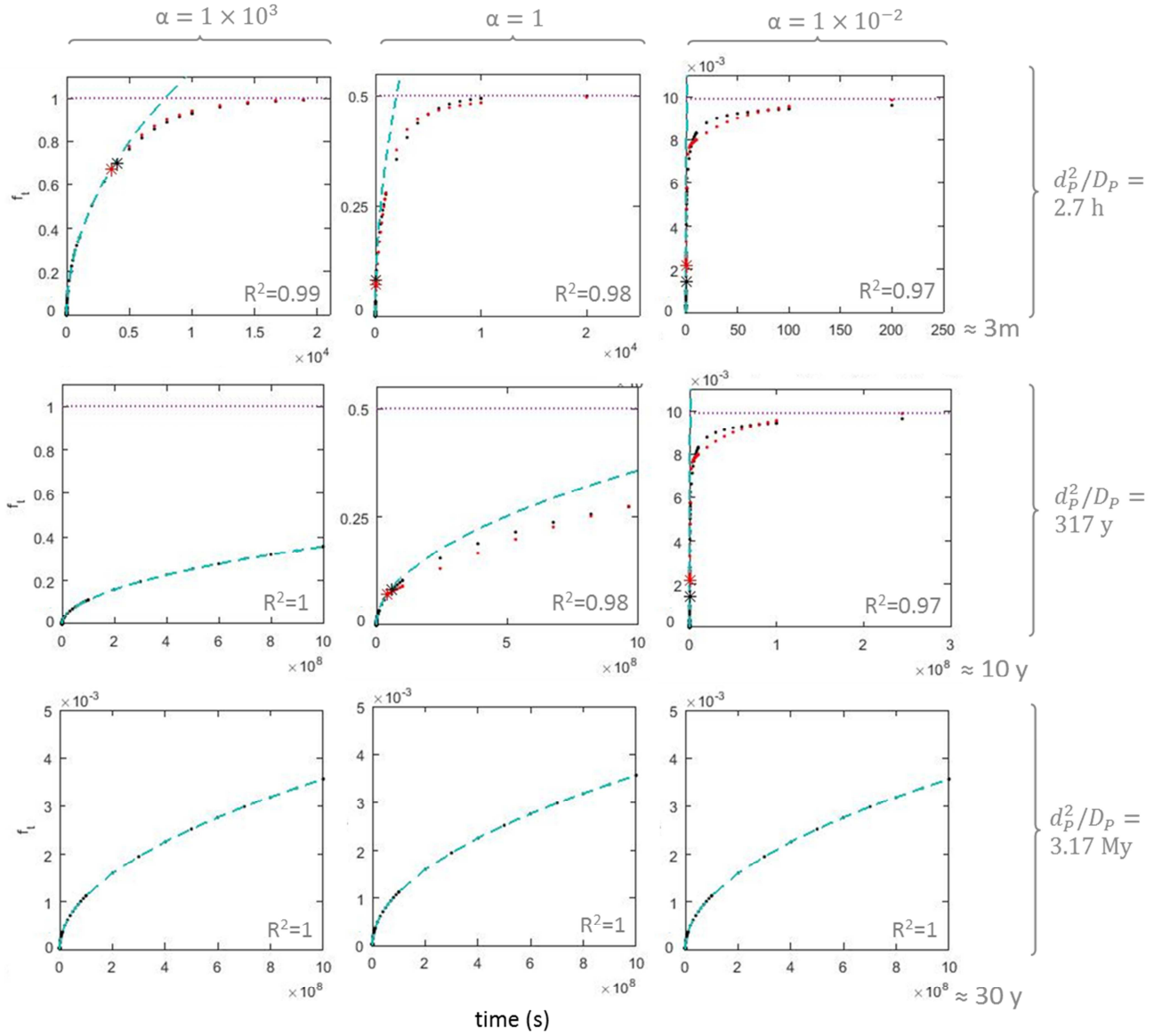
<table>
<tr><td colspan="2">Model
$$f_{t,p} = \begin{cases} \frac{2}{d_p} \times (D_p\ \mathrm{t_d}/\pi)^{\frac{1}{2}} \text{ eq(2)} & \text{if } \mathrm{t_d} \le t_d^*, \text{ else} \\ y_{t_d^*} + \left(\frac{\alpha}{1+\alpha} - y_{t_d^*}\right) \times \left(A \times \left(1 - \mathrm{e}^{-B \times \beta \times (\mathrm{t_d} - t_d^*)}\right) + (1-A) \times \left(1 - \mathrm{e}^{-C \times \beta (\mathrm{t_d} - t_d^*)}\right)\right) \end{cases} \quad (4)$$
where $y_{t_d^*} = \frac{2}{d_p} \times (D_p t_d^*/\pi)^{\frac{1}{2}}$</td></tr>
<tr><td>Diffusion coefficient</td><td>$$D_P = D_o \exp\left(A_P - 0.1351 MW^{\frac{2}{3}} + 0.003 MW - \frac{10454}{T}\right)\left(\frac{cm^2}{s}\right) \quad (5)$$
where $A_P = A'_P - \frac{\tau}{T}, D_o = 1\ \mathrm{m^2/s} = 10^4\ \mathrm{cm^2/s}$ and
$R = 8.3145\ \mathrm{J\ mol^{-1}\ K^{-1}}$.</td></tr>
<tr><td>Contact time when eq (2) deviates from eq (1) >1%</td><td>$$t_d^* = \begin{cases} \frac{d_P^2}{D_P}\left(\frac{r_1}{1 + r_2 e^{r_3 \times \log(\alpha)}}\right) & \text{for } \alpha \le 0.2 \\ \frac{d_P^2}{D_P} r_4 e^{r_5 \times \log(\alpha)} & \text{for } \alpha > 0.2 \end{cases} \text{ (s)} \quad (6)$$
R^2=0.99 when the values and the 95% confidence interval (CI) are:
r_1(95% CI)=0.3552 (0.3549, 0.3555)
r_2 (95% CI)=85.88 (83.99, 87.77),
r_3(95% CI)=-3.506 (-3.524, -3.488),</td></tr>
</table>

	r_4(95% CI)=8.495^{E}-3 (8.375^{E}-3, 8.616^{E}-3) r_5(95% CI)=4.458 (4.445, 4.47).
Slope factor (β), approximation of the slope (derivative) of eq (2) at time t_d*	$\beta = \frac{1}{d_P}\sqrt{\frac{D_P}{\pi t_d^*}} \times \left(\underbrace{\frac{\alpha}{1+\alpha}}_{eq\ (3)} - \underbrace{\frac{2}{d_p} \times (D_p\, t_d^*/\pi)^{\frac{1}{2}}}_{eq\ (2)\ at\ t_d^*} \right)^{-1}$ (s^{-1}) (7)
Coefficients A, B, and C	$A(x_1) = \begin{cases} 0.7 \text{ for } x_1 < 0.7 \\ 1 \text{ for } x_1 > 1 \\ x_1 \text{ elsewhere;} \end{cases}$ where $x_1 = 10^{0.12\ log(\alpha) + log\ 0.8}$ (8a) $B(x_2) = \begin{cases} 0.3 \text{ for } x_2 < 0.3 \\ 0.9 \text{ for } x_2 > 0.9 \\ x_2 \text{ elsewhere;} \end{cases}$ where $x_2 = 10^{0.22\ log(\alpha) + log\ 0.5}$ (8b) $C(x_3) = \begin{cases} 0.004 \text{ for } x_3 < 0.3 \\ 1 \text{ for } x_3 > 1 \\ x_3 \text{ elsewhere;} \end{cases}$ where $x_3 = 10^{0.7\ log(\alpha) + log\ 0.08}$ (8c)
Partition coefficient between package and food.	$\log K_{P,F} = m \times \log(K_{ow}) - b$ (9) where $m = -0.0085 \times \text{EtOH} - \text{eq} + 0.876$, and b= 1.05.[#]

[#]Data were not available for chemicals with log K_{ow} >≈5, 8, 18 when the EtOH-eq is ≈10, 50, 95% respectively, and the model accuracy in this range is thus unknown.

HT Model performance: Figure 2 demonstrates the resulting model performance across a wide range of permutations of α, D_P, and d_P, where the model behaviour is specific to combinations of α and CTM, within a feasible contact duration between package and food (i.e. <30y). Simulations were chosen within realistic values of α and CTM based on observed ranges of partition coefficients, diffusion coefficients and packaging thicknesses (Piringer and Baner 2008). Figure 2 is organised in rows and columns, where alpha decreases from the first to third column, and where the CTM increases from first to third row. When alpha is large the potential migrated fraction approaches 1, and as alpha decreases (see first to third column) so does the migrated fraction. As CTM increases between the first and third rows, the time to reach full migration (seen as the curve flattening at a

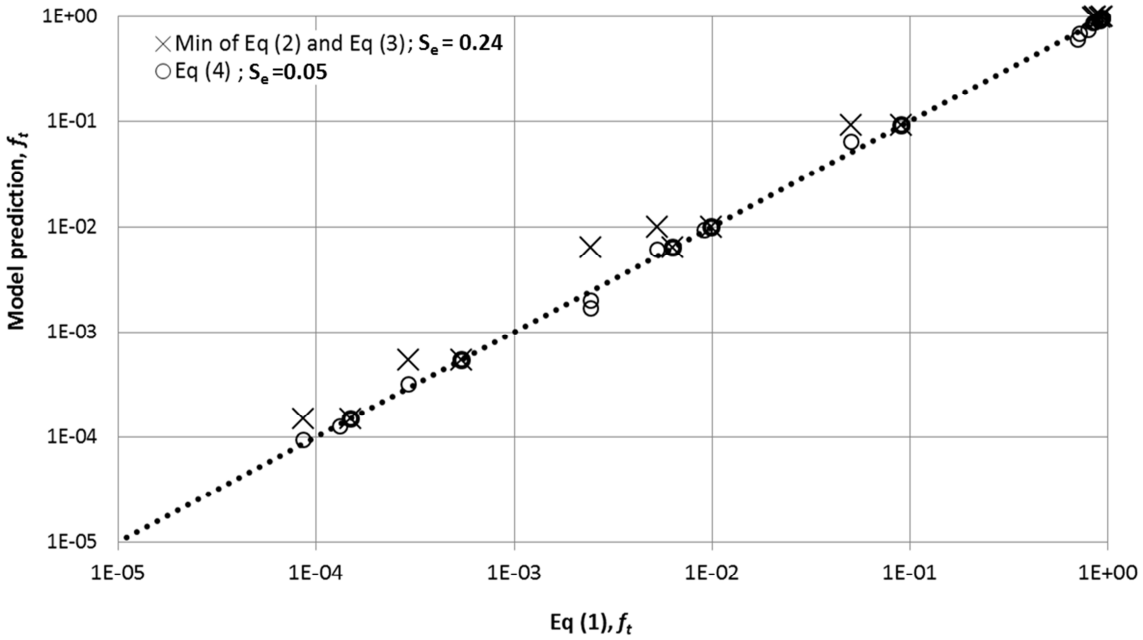
plateau) also increases. For each CTM (see first to third column for each row) the model plateaus at earlier contact times when there is a lower α value which corresponds to a lower equilibrium value. For each CTM (rows) the model plateaus earlier with low α values and subsequent equilibrium value (columns). Figure 2 also demonstrates that the HT model (in red) fits very well the original model (in black) with R^2 between 0.97 and 1, across a wide range of relevant time scales from a few minutes to 30 years and input parameter combinations. The HT model represents a substantial improvement compared to the combination of the minimum value of the short-term diffusion dominated model (in green) and the long-term equilibrium value (pink dotted line) that may over-estimates f_t by a factor of 3 (Figure 3). The points plotted in the figure represent the maximum over-estimation which always occurs when eq (2) intersects eq (3) (also see Figure 1). SI Table S3 provides example combinations of D_P, and d_P (infinite combinations are possible) to obtain the CTMs that were simulated.



392

393 Figure 2. Comparison between the migrated fraction, f_t, predicted by the HT model (Table 1) after the
394 deviation point, t_d* (red solid line), with f_t predicted by the original model, eq (1) (black solid line). A
395 range of combinations of α and characteristic times (d_P^2/D_p, converted to relevant units, where My is
396 millions of years) were simulated to cover a feasible span of scenarios and R^2 were obtained. The
397 diffusion-based model, eq (2) (turquoise dashed line), and the equilibrium-based model, eq (3) (pink

398 dotted line) are also shown. Eq (2) and eq (1) are >99% equal until t_d* (black asterisk); the red asterisk
399 is the predicted t_d* where the double exponential form begins.



400

401 Figure 3. Comparison between the migrated fraction f_t predicted by the detailed model eq (1), by the
402 HT model (Table 1) and by taking the minimum of the diffusion-based model eq (2) and the
403 equilibrium-based model eq (3). Standard error, S_e, on the logarithmic scale is indicated with the
404 legend.

405

406 **3.2 Model parametrization**

407 Determination of the diffusion and partition coefficients, D_P and $K_{P,F}$, are essential to model migration
408 and key parameters in all model eqs (1) to (3) and in the HT model described in Table 1. For D_P we
409 used the established equation presented by Begley et al. (2005) as shown in equation (5), but when
410 available a measured value or more precise model should be used for this parameter. Eq (9), Table 1,
411 provides the model to estimate the log-log linear approximation of $K_{P,F}$. SI Figure S6 compares this
412 approximation with the empirical data reported in Table 2 of Ozaki et al. 2010 (Table 2),
413 demonstrating a good resulting correlation. The performance of the model on the log-scale was
414 described by standard error (S_e), the coefficient of determination (R^2), and the squared geometric
415 standard deviation (GSD^2); assuming with a log-normal distribution of uncertainty around the
416 modelled value, the product of the modelled value and GSD^2 is equal to the 97.5%-ile and the
417 quotient of the modelled value and GSD^2 is equal to the 2.5%-ile of the expected data uncertainty
418 distribution (Heijungs and Frischknecht 2004).

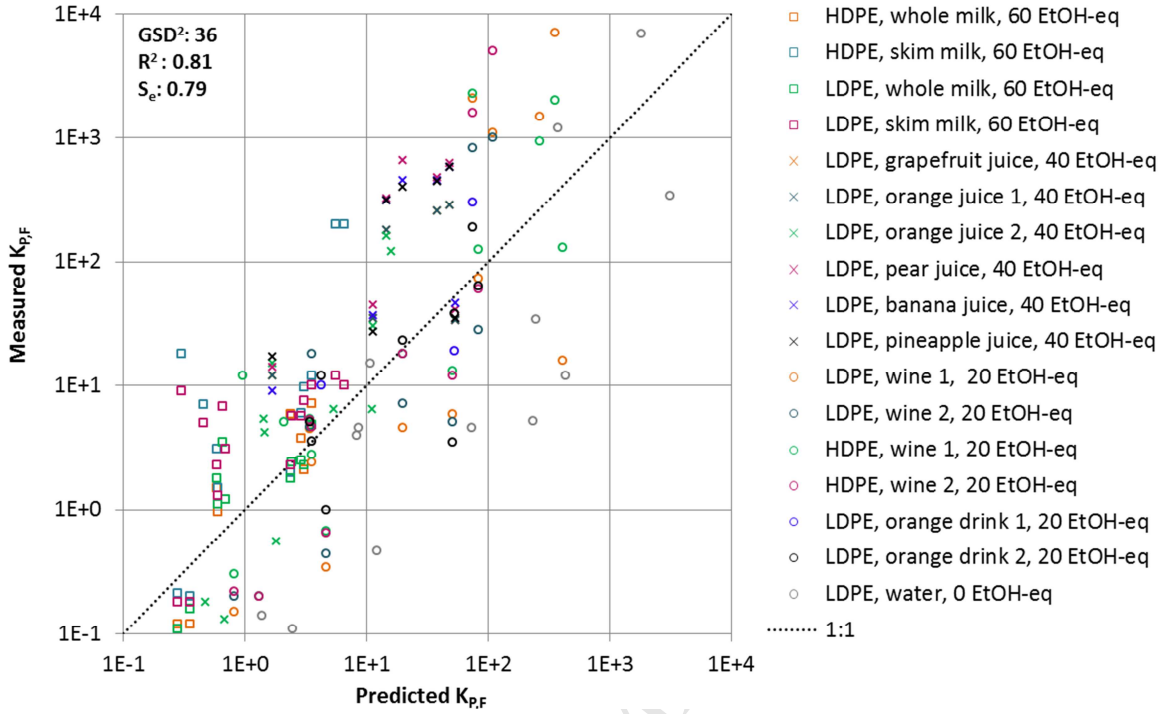


Figure 4. Comparison of the predictions of partition coefficients $K_{P,F}$ by the HT model with empirical data from Mercea 2008; dotted line is the 1:1 diagonal; the squared geometric standard deviation (GSD^2), standard error (S_e) and coefficient of determination (R^2) are evaluated on the log-scale.

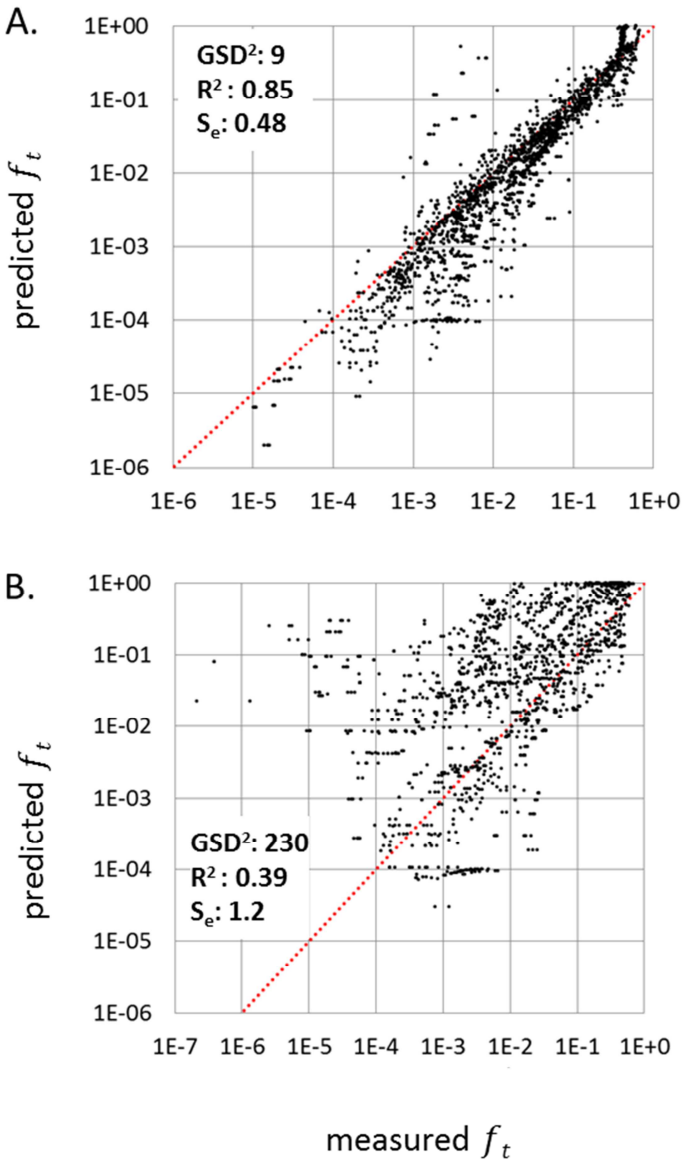
Figure 4 demonstrates an external validation of the developed $K_{P,F}$ model compared with empirical data for 17 chemicals from Appendix II Piringer & Baner (2008) (Mercea 2008) with various food types and two polymers at 23 ^{o}C (Figure 4). The considered chemicals' MWs ranged from 94 to 220 g/mol and from log K_{ow} 1.3 to 5.2. The performance of the $K_{P,F}$ model was reasonable for both LDPE and HDPE, likely because these polymers have similar properties influencing partitioning (e.g. polarity) (Ozaki et al. 2010). The applicability of the model for polymers other than LDPE and HDPE is unknown at this time and should be explored in future work. The influence of $K_{P,F}$ uncertainty can be

understood by examining the influence of α on the ultimate equilibrium value, where α is a function of $K_{P,F}$ and the volumes of food and packaging material. The sensitivity of the equilibrium value to α depends on the magnitude of α. Since equilibrium is determined as α / (1 + α), eq (3), there is maximum a factor 2 difference between the equilibrium values of any α >= 1 (which range between 0.5 and 1). This means uncertainty of $K_{P,F}$ becomes less important as the equilibrium value increases. When α <=0.1 the sensitivity of the equilibrium value is mirrored, where a factor 10 difference in α (or $K_{P,F}$ holding all else constant) results in nearly a factor 10 difference in the equilibrium value. This means when equilibrium is low the uncertainty on $K_{P,F}$ is more important.

3.3 High-throughput migration modelling – external validation

The calculation speed for the HT migration model developed in this paper and listed in Table 1 is nearly instantaneous, and the full model was programmed in a spreadsheet. Of the 4,492 FDA data points with data available for parameterization 1,428 were excluded due to high K_{ow} outside of the range of the empirical data used for determining $K_{P,F}$. We first applied the HT model (Table 1) with the *measured* diffusion coefficients reported in the FDA database (SI Figure S6), considering all data points (GSD^2 = 24, R^2 = 0.6, S_e = 0.7). Two sets of data points from one experimental data set referred to as "Models for the Migration of Low Molecular Weight Additives in Polyolefins. National Bureau of Standards. Report NBSIR 81-2264, April, 1981.", corresponding to experiments for a chemical called BHT in DEHP migration to corn oil and ethanol and dotriacontane in corn oil were clear outliers. The reported diffusion coefficients caused an unexplainable vertical shift (SI Figure S7) from the trend observed for the rest of the data, including other data for the same chemicals, polymers and simulants, suggesting analytical issues from this experimental dataset. We therefore also removed

these 744 points for these two chemicals of this dataset. Screening was finally performed for the remaining 2,320 data points (Figure 5) and when using measured data for the diffusion coefficient (Figure 5A), the uncertainty was minimal (GSD^2=8, R^2 =0.87, S_e= 0.48).



455 Figure 5A-B. Prediction of $m_{i,t}/m_{i,0}$ using the developed HT model (Table 1) compared to empirical
456 data from US FDA, where either the measured (Figure 5A) or modelled D_P, eq (5) was used (Figure
457 5B). Dotted red line represents the 1:1 diagonal; the squared geometric standard deviation (GSD^2),
458 standard error (S_e) and coefficient of determination (R^2) values are evaluated on the log-scale.

459 Using eq (2) and eq (3) to model these points yielded the same results as applying the approach in
460 Table 1, because the experiments in the FDA study were all in the short-term contact duration
461 range—and in fact are reasonably estimable by only eq (2). The US FDA empirical dataset provides
462 estimated diffusion coefficients, therefore experiments were likely intentionally restricted to be in the
463 range of diffusion-dominating behaviour. To our knowledge there is no available empirical dataset to
464 test the model that covers a full range of measured values shifting from diffusion-dominated to
465 partition-dominated behaviour (as experiments are usually designed to obtain either of these
466 parameters).

467 When the HT model (Table 1) was applied with *modelled diffusion coefficients,* eq (5), the 95^{th}
468 percentile distribution increased by more than an order of magnitude on either side of the modelled
469 point and the goodness of fit fell (Figure 5B) (GSD^2 =230, R^2 =0.49, S_e = 1.2). This dramatic increase in
470 uncertainty is thereby directly attributable to the diffusion coefficient model. To reduce the
471 uncertainty of diffusion modelling, topological molecular descriptors (e.g. molecular volume) are an
472 area of interest (Fang and Vitrac 2017); however, more accurate models using topological input
473 parameters have not yet been operationalised for rapid HT modelling. Therefore, improving HT-
474 compatible modelling of the diffusion coefficient, for example through quantitative property-property

475 relationship modelling (Huang et al. 2017b), is necessary for future HT models estimating migration of
476 chemicals from packaging into food.

477 Eq (1) and the resulting HT approach is mathematically valid when the matrix of the food poses no
478 resistance to diffusion and is continuously mixed, e.g. valid for fluids, which is the most studied and
479 empirically validated scenario (Pocas 2008; Piringer and Baner 2008). Most of the empirical data used
480 to validate the model is from liquid foods (e.g. beverages) and only several experiments were
481 available for non-liquid foods, mayonnaise and chocolate. Given these limited data, there was also
482 good agreement between the model and the estimates of the migration of chemicals from packaging
483 into foods (SI Figure S9). Further work would be required to develop and test the model against solid
484 and dry foods; applying a multiplying ratio of the diffusion coefficients between food and polymer
485 may be useful in future approaches to adjust the model (Piringer and Baner 2008).

486 ## 4. Conclusion

487 High-throughput (HT) modelling approaches were developed to estimate the fraction of an organic
488 chemical migrating from a polymeric food contact material into a food. The primary aim was to
489 operationalize migration modelling, e.g. eqs (1)-(3), to be suitable for decision-support tools that
490 require rapid calculation of best-estimates of migration. Setting the partition coefficient between
491 packaging and food equal to one (which we found was not a universal “worst-case” scenario) can lead
492 to grossly misestimating the equilibrium value. Therefore, we also developed methods to estimate
493 the partition coefficient to ensure more accurate HT methods. A main outcome was furthermore, a
494 method to more precisely determine the timespan for which an existing simple, diffusion-based
495 model, eq (2), is valid. We determined this simple model is valid when the contact duration between

496 the food and package is less than the developed prediction for t_d* (eq 6, Table 1), which can range
497 from fractions of a second to several years depending on the input parameters and can be predicted
498 as a function of α and CTM – the characteristic time of migration.

499 By providing a method to determine t_d*, the timespan where eq (2) is valid, and additionally
500 developing a method to estimate migration after t_d*, the developed HT model (Table 1) is valid over
501 all relevant timespans. The new HT model also showed good agreement with eq (1) over a full range
502 of input parameters and agreement improved as the parameter α increased (meaning the equilibrium
503 concentration in food increased). The developed HT model offers substantial improvement compared
504 to the combination of the minimum value of the diffusion-based model eq (2), and the equilibrium
505 value eq (3), that may otherwise over-estimate f_t by a factor of 3 after t_d* and before equilibrium is
506 achieved. Additionally, our model was more accurate by several orders of magnitude than using eq (1)
507 with a limited number of tabulated roots at short time scales; therefore the developed HT model is
508 preferred to eq (1) for comparative assessments that aim at average rather than conservative
509 estimates. Furthermore, the model demonstrated good agreement with measured data, especially
510 when using a measured diffusion coefficient. When a modelled diffusion coefficient was used, there
511 was a drastic increase in uncertainty, underscoring the importance of improving diffusion coefficient
512 modelling.

513 The developed model, as well as eq (1), rely on α which is a direct function of the partition coefficient
514 between a polymer and a food, $K_{P,F}$. The model we developed, eq (9), to estimate $K_{P,F}$ as a function of
515 the chemical K_{ow} and the food's assigned ethanol-equivalency, EtOH-eq, also had good agreement
516 with the empirical data (R^2=0.81) which are limited to LDPE and HDPE polymers. The approach is

517 similar to other models (Seiler et al. 2014), however, we additionally provide the equation to support
518 application in future uses.

519 The developed model is intended for future use in decision support tools that consider exposure to
520 chemicals in food packaging materials in a variety of scenarios, for example in Life Cycle Assessment
521 (LCA) or high-throughput risk-based screening (HTRS) (Shin et al. 2015; Jolliet et al. 2015b). In such
522 decision support assessments the model could be combined with the initial chemical mass in a food
523 packaging material in order to estimate the migrated mass and subsequent exposure. Furthermore, in
524 order to estimate risk exposure estimates can be combined with toxicity information, e.g. if available
525 through high-throughput screening (Karmaus et al. 2016) and relevant dosimetry adjustments
526 (Wetmore et al. 2015). The initial concentration of chemicals in various consumer products are
527 becoming increasingly available through databases (Goldsmith et al. 2014); however, concentrations
528 of chemicals in packaging are not yet available. Future research is required to fill this concerning data
529 gap, e.g. through rapid analytical identification methods or function-based chemical concentration
530 modelling, as has been recently performed for cosmetics (Isaacs et al. 2016).

531 The model was specifically designed to address the need for estimating the product intake fraction
532 (Jolliet et al. 2015a) (Section 2.1) of food contact materials in LCA. Recent studies have underscored
533 trade-offs between environmental impacts of food packaging systems and exposure to potentially
534 toxic chemicals in food packaging materials (Lee et al. 2014; Yuan et al. 2016; Leslie et al. 2016).
535 Considering exposure to chemicals in packaging within LCA could, for example, help ensure that
536 system or packaging designs aiming to minimize environmental impacts (e.g. greenhouse gas
537 emissions or resource use) do not unintentionally increase exposure to hazardous chemicals in

packaging, and vice versa that system or product designs to minimize migration and exposure to hazardous substances do not increase environmental impacts.

In all, this study presents a rapid method to provide best-estimates of migration of chemicals from packaging with a first focus on organic chemicals in polymeric food packaging. Future work could extend this approach to other food contact materials (e.g. paper and board) and chemical types (e.g. nanoparticles or inorganic chemicals). Future focus on diffusion coefficient modelling, for polymers and other material types, should also be a priority to improve the accuracy of migration modelling in general. Additionally, future work should focus on identifying data availabilities that will be required for application of the model in decision support tools, such as the initial chemicals in packaging and toxicity of these chemicals.

Acknowledgements

This work was financially supported by the Marie Curie projects Tox-Train (grant agreement no. 285286) and Quan-Tox (grant agreement no. 631910) funded by the European Commission under the Seventh Framework Programme.

References

Apelberg BJ, Witter FR, Herbstman JB, et al (2007) Cord Serum Concentrations of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Weight and Size at Birth. Environ Health Perspect 115:1670–1676. doi: 10.1289/ehp.10334

Barnes K, Sinclair R, Watson D (2006) Chemical Migration and Food Contact Materials. Woodhead Publishing

558 Begley T, Castle L, Feigenbaum A, et al (2005a) Evaluation of migration models that might be used in support of
559 regulations for food-contact plastics. Food Addit Contam 22:73–90. doi: 10.1080/02652030400028035

560 Begley TH, White K, Honigfort P, et al (2005b) Perfluorochemicals: Potential sources of and migration from food
561 packaging. Food Addit Contam 22:1023–1031. doi: 10.1080/02652030500183474

562 Beretta C, Stoessel F, Baier U, Hellweg S (2013) Quantifying food losses and the potential for reduction in
563 Switzerland. Waste Manag 33:764–773. doi: 10.1016/j.wasman.2012.11.007

564 Biedermann M, Grob K (2013a) Assurance of safety of recycled paperboard for food packaging through
565 comprehensive analysis of potential migrants is unrealistic. J Chromatogr A 1293:107–119. doi:
566 10.1016/j.chroma.2013.04.009

567 Biedermann M, Grob K (2013b) Assurance of safety of recycled paperboard for food packaging through
568 comprehensive analysis of potential migrants is unrealistic. J Chromatogr A 1293:107–119. doi:
569 10.1016/j.chroma.2013.04.009

570 Brandsch J (2000) Modelling of additive diffusion coefficients in polyolefins, Washington, DC. American
571 Chemical Society

572 Brandsch J, Mercea P, Rüter M, et al (2002) Migration modelling as a tool for quality assurance of food
573 packaging. Food Addit Contam 19:29–41. doi: 10.1080/02652030110058197

574 Buzby JC, Farah-Wells H, Hyman J (2014) The Estimated Amount, Value, and Calories of Postharvest Food
575 Losses at the Retail and Consumer Levels in the United States. Social Science Research Network,
576 Rochester, NY

577 Cao X-L (2010) Phthalate Esters in Foods: Sources, Occurrence, and Analytical Methods. Compr Rev Food Sci
578 Food Saf 9:21–43. doi: 10.1111/j.1541-4337.2009.00093.x

579 Chang JCS, Guo Z (1992) Characterization of Organic Emissions from a Wood Finishing Product – Wood Stain.
580 Indoor Air 2:146–153. doi: 10.1111/j.1600-0668.1992.03-23.x

581 Crank J (1975) The Mathematics of Diffusion, 2nd edn. Clarendon Press, Oxford University Press, Great Britain

582 Csiszar SA, Ernstoff AS, Fantke P, Jolliet O (2016a) Stochastic modelling of near-field exposure to parabens in
583 personal care products. J Expo Sci Environ Epidemiol. doi: 10.1038/jes.2015.85

584 Csiszar SA, Meyer DE, Dionisio KL, et al (2016b) Conceptual Framework To Extend Life Cycle Assessment Using
585 Near-Field Human Exposure Modelling and High-Throughput Tools for Chemicals. Environ Sci Technol
586 50:11922–11934. doi: 10.1021/acs.est.6b02277

587 Delmaar JE, Bokkers BGH, ter Burg W, van Engelen JGM (2013) First tier modelling of consumer dermal
588 exposure to substances in consumer articles under REACH: A quantitative evaluation of the ECETOC
589 TRA for consumers tool. Regul Toxicol Pharmacol 65:79–86. doi: 10.1016/j.yrtph.2012.10.015

590 Ernstoff AS, Fantke P, Csiszar SA, et al (2016) Multi-pathway exposure modelling of chemicals in cosmetics with
591 application to shampoo. Environ Int 92–93:87–96. doi: 10.1016/j.envint.2016.03.014

592 European Bureau for Conservation and Development (2015) Ensuring a non-toxic circular economy Promotion
593 of material cycles without hazardous substance. European Parliament, Brussels

594 Evans RM, Martin OV, Faust M, Kortenkamp A (2016) Should the scope of human mixture risk assessment span
595 legislative/regulatory silos for chemicals? Sci Total Environ 543, Part A:757–764. doi:
596 10.1016/j.scitotenv.2015.10.162

597 Fang X, Vitrac O (2017) Predicting diffusion coefficients of chemicals in and through packaging materials. Crit
598 Rev Food Sci Nutr 57:275–312. doi: 10.1080/10408398.2013.849654

599 Fantke P, Ernstoff AS, Huang L, et al (2016) Coupled near-field and far-field exposure assessment framework for
600 chemicals in consumer products. Environ Int. doi: 10.1016/j.envint.2016.06.010

601 FDA (2015a) CEDI Database.
602 http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm. Accessed 6
603 Apr 2016

604 FDA (2015b) Recycled Plastics in Food Packaging.
605 http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/RecycledPlastics/default.htm.
606 Accessed 15 Aug 2016

607 FDA (2016) Guidance Documents & Regulatory Information by Topic - Guidance for Industry: Preparation of
608 Premarket Submissions for Food Contact Substances: Chemistry Recommendations.
609 http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm08181
610 8.htm. Accessed 16 Sep 2015

611 Flanigan L, Frischknecht R, Montalbo T (2013) An analysis of life cycle assessment in packaging for food and
612 beverage applications.

613 Geens T, Aerts D, Berthot C, et al (2012) A review of dietary and non-dietary exposure to bisphenol-A. Food
614 Chem Toxicol 50:3725–3740.

615 Geueke B, Wagner CC, Muncke J (2014) Food contact substances and chemicals of concern: a comparison of
616 inventories. Food Addit Contam Part -Chem Anal Control Expo Risk Assess 31:1438–1450. doi:
617 10.1080/19440049.2014.931600

618 Goldsmith M-R, Grulke CM, Brooks RD, et al (2014) Development of a consumer product ingredient database
619 for chemical exposure screening and prioritization. Food Chem Toxicol 65:269–279. doi:
620 10.1016/j.fct.2013.12.029

621 Hauschild MZ (2005) Assessing Environmental Impacts in a Life-Cycle Perspective. Env Sci Technol 39:81A–88A.
622 doi: 10.1021/es053190s

623 Heijungs R, Frischknecht R (2004) Representing Statistical Distributions for Uncertain Parameters in LCA.
624 Relationships between mathematical forms, their representation in EcoSpold, and their representation
625 in CMLCA (7 pp). Int J Life Cycle Assess 10:248–254. doi: 10.1065/lca2004.09.177

626 Hellweg S, Milà i Canals L (2014) Emerging approaches, challenges and opportunities in life cycle assessment.
627 Science 344:1109–1113. doi: 10.1126/science.1248361

628 Hoekstra EJ, Brandsch R, Dequatre C, et al (2015) Practical guidelines on the application of migration modelling
629 for the estimation of specific migrationE.J. Hoekstra, R. Brandsch, C. Dequatre, P. Mercea, M.R. Milana,
630 A. Störmer, X. Trier, O. Vitrac A. Schäfer and C. Simoneau; European Commission, Joint Research Centre

631 Huang L, Jolliet O (2016) A parsimonious model for the release of volatile organic compounds (VOCs)
632 encapsulated in products. Atmos Environ 127:223–235. doi: 10.1016/j.atmosenv.2015.12.001

633 Huang L, Ernstoff A, Fantke P, et al (2017a) A review of models for near-field exposure pathways of chemicals in
634 consumer products. Sci Total Environ 574:1182–1208. doi: 10.1016/j.scitotenv.2016.06.118

635 Huang L, Fantke P, Ernstoff A, Jolliet O (2017b) A Quantitative Property-Property Relationship for the Internal
636 Diffusion Coefficients of Organic Compounds in Solid Materials. Indoor Air. doi: 10.1111/ina.12395

637 Hunt RG, Franklin WE (1996) LCA — How it came about. Int J Life Cycle Assess 1:4–7. doi: 10.1007/BF02978624

638 Isaacs KK, Glen WG, Egeghy P, et al (2014) SHEDS-HT: An Integrated Probabilistic Exposure Model for
639 Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources. Environ Sci Technol 48:12750–
640 12759. doi: 10.1021/es502513w

641 Isaacs KK, Goldsmith M-R, Egeghy P, et al (2016) Characterization and prediction of chemical functions and
642 weight fractions in consumer products. Toxicol Rep 3:723–732. doi: 10.1016/j.toxrep.2016.08.011

643 Jolliet O, Ernstoff AS, Csiszar SA, Fantke P (2015a) Defining Product Intake Fraction to Quantify and Compare
644 Exposure to Consumer Products. Environ Sci Technol 49:8924–8931. doi: 10.1021/acs.est.5b01083

645 Jolliet O, Saade M, Shaked S, Jolliet A (2015b) Environmental Life Cycle Assessment. Taylor & Francis

646 Karmaus AL, Filer DL, Martin MT, Houck KA (2016) Evaluation of food-relevant chemicals in the ToxCast high-
647 throughput screening program. Food Chem Toxicol 92:188–196. doi: 10.1016/j.fct.2016.04.012

648 Lee J, Pedersen AB, Thomsen M (2014) The influence of resource strategies on childhood phthalate exposure—
649 The role of REACH in a zero waste society. Environ Int 73:312–322. doi: 10.1016/j.envint.2014.08.003

650 Leslie HA, Leonards PEG, Brandsma SH, et al (2016) Propelling plastics into the circular economy — weeding
651 out the toxics first. Environ Int 94:230–234. doi: 10.1016/j.envint.2016.05.012

652 Mercea P (2008) Appendix II: Partition Coefficients. In: Piringer OG, Baner AL (eds) Plastic Packaging. Wiley-VCH
653 Verlag GmbH & Co. KGaA, pp 89–121

Mercea P (2000) Models for diffusion in polymers. In: Piringer O-G, Baner AL (eds) Plastic Packaging Materials for Food. Wiley-VCH Verlag GmbH, pp 125–157

Muncke J, Myers JP, Scheringer M, Porta M (2014) Food packaging and migration of food contact materials: will epidemiologists rise to the neotoxic challenge? J Epidemiol Community Health 68:592–594. doi: 10.1136/jech-2013-202593

Neltner TG, Alger HM, Leonard JE, Maffini MV (2013) Data gaps in toxicity testing of chemicals allowed in food in the United States. Reprod Toxicol 42:85–94. doi: 10.1016/j.reprotox.2013.07.023

Oldring PKT, Castle L, O'Mahony C, Dixon J (2014a) Estimates of Dietary Exposure to Bisphenol A (BPA) from Light Metal Packaging using Food Consumption and Packaging usage Data: A Refined Deterministic Approach and a Fully Probabilistic (FACET) Approach. Food Addit Contam Part Chem Anal Control Expo Risk Assess 31:466–489. doi: 10.1080/19440049.2013.860240

Oldring PKT, O'Mahony C, Dixon J, et al (2014b) Development of a new modelling tool (FACET) to assess exposure to chemical migrants from food packaging. Food Addit Contam Part Chem Anal Control Expo Risk Assess 31:444–465. doi: 10.1080/19440049.2013.862348

Ozaki A, Gruner A, Störmer A, et al (2010) Correlation between Partition Coefficients Polymer/Food Simulant, KP,F, and Octanol/Water, Log POW — a New Approach in support of Migration Modelling and Compliance Testing. Dtsch Lebensm-Rundsch 106:203–208.

Piringer OG, Baner AL (2008) Plastic Packaging Materials for Food: Barrier Function, Mass Transport, Quality Assurance, and Legislation. John Wiley & Sons

Pocas MF (2008) A Critical Survey of Predictive Mathematical Models for Migration from Packaging. Crit Rev FOOD Sci Nutr 48:913–928. doi: 10.1080/10408390701761944

Pocas MF, Oliveira JC, Brandsch R, Hogg T (2012) Analysis of Mathematical Models to Describe the Migration of Additives from Packaging Plastics to Foods. J Food Process Eng 35:657–676. doi: 10.1111/j.1745-4530.2010.00612.x

Price N, Chaudhry Q (2014) Application of in silico modelling to estimate toxicity of migrating substances from food packaging. Food Chem Toxicol 71:136–141. doi: 10.1016/j.fct.2014.05.022

Rosenbaum RK, Bachmann TM, Gold LS, et al (2008) USEtox—the UNEP-SETAC toxicity model: recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. Int J Life Cycle Assess 13:532–546. doi: 10.1007/s11367-008-0038-4

Rudel RA, Gray JM, Engel CL, et al (2011) Food Packaging and Bisphenol A and Bis(2-Ethyhexyl) Phthalate Exposure: Findings from a Dietary Intervention. Environ Health Perspect 119:914–920. doi: 10.1289/ehp.1003170

Seiler A, Bach A, Driffield M, et al (2014) Correlation of foodstuffs with ethanol–water mixtures with regard to the solubility of migrants from food contact materials. Food Addit Contam Part A 31:498–511. doi: 10.1080/19440049.2014.880518

689 Shin H-M, Ernstoff AS, Arnot JA, et al (2015) Risk-based High-Throughput Chemical Screening and Prioritization
690 using Exposure Models and in Vitro Bioactivity Assays. Environ Sci Technol 49:6760–6771. doi:
691 10.1021/acs.est.5b00498

692 Shin H-M, McKone TE, Bennett DH (2012) Intake fraction for the indoor environment: A tool for prioritizing
693 indoor chemical sources. Environ Sci Technol 46:10063–10072.

694 Siracusa V, Ingrao C, Lo Giudice A, et al (2014) Environmental assessment of a multilayer polymer bag for food
695 packaging and preservation: An LCA approach. Food Res Int 62:151–161. doi:
696 10.1016/j.foodres.2014.02.010

697 Tehrany EA, Desobry S (2004) Partition coefficients in food/packaging systems: a review. Food Addit Contam
698 Part -Chem Anal Control Expo Risk Assess 21:1186–1202. doi: 10.1080/02652030400019380

699 Tehrany EA, Desobry S (2005) Comparison between the different calculation methods of partition coefficient of
700 aroma compounds with a difference chemical classes in octanol/water system. Sci Aliments 25:23–36.

701 Tehrany EA, Fournier F, Desobry S (2006) Simple method to calculate partition coefficient of migrant in food
702 simulant/polymer system. J Food Eng 77:135–139. doi: 10.1016/j.jfoodeng.2005.06.055

703 Tittlemier SA, Pepper K, Seymour C, et al (2007) Dietary Exposure of Canadians to Perfluorinated Carboxylates
704 and Perfluorooctane Sulfonate via Consumption of Meat, Fish, Fast Foods, and Food Items Prepared in
705 Their Packaging. J Agric Food Chem 55:3203–3210. doi: 10.1021/jf0634045

706 Wambaugh JF, Setzer RW, Reif DM, et al (2013) High-Throughput Models for Exposure-Based Chemical
707 Prioritization in the ExpoCast Project. Environ Sci Technol 47:8479–8488. doi: 10.1021/es400482g

708 Wetmore BA, Wambaugh JF, Allen B, et al (2015) Incorporating High-Throughput Exposure Predictions with
709 Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. Toxicol Sci 148:121–136.
710 doi: 10.1093/toxsci/kfv171

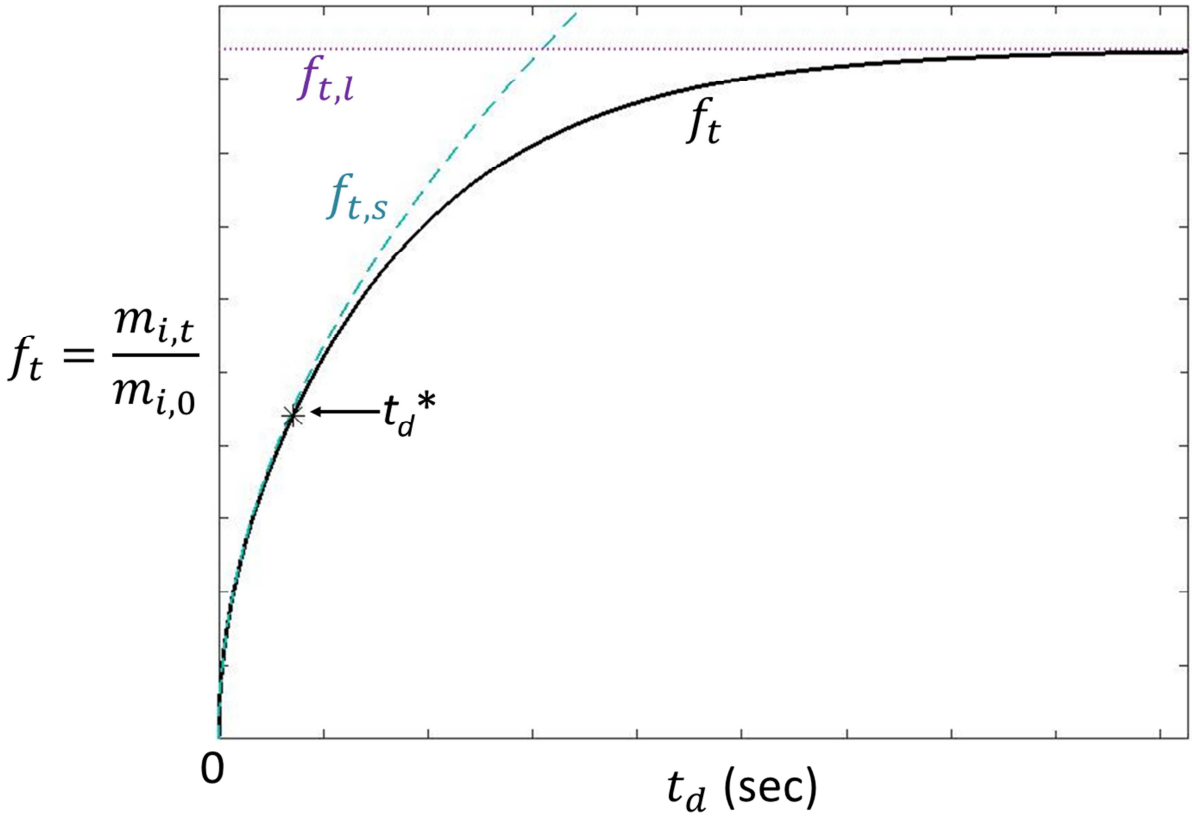
711 Williams H, Wikström F (2011) Environmental impact of packaging and food losses in a life cycle perspective: a
712 comparative analysis of five food items. J Clean Prod 19:43–48. doi: 10.1016/j.jclepro.2010.08.008

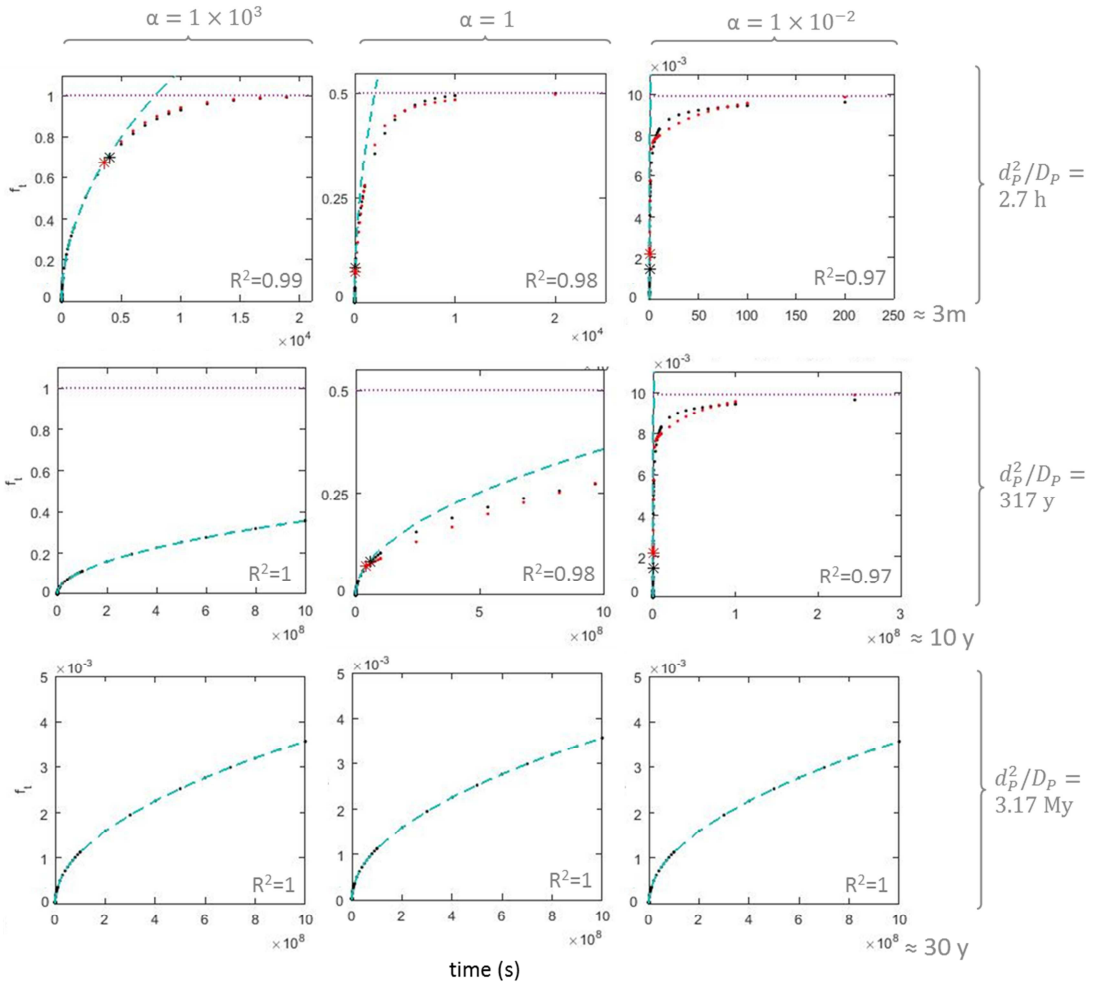
713 Williams H, Wikström F, Otterbring T, et al (2012) Reasons for household food waste with special attention to
714 packaging. J Clean Prod 24:141–148. doi: 10.1016/j.jclepro.2011.11.044

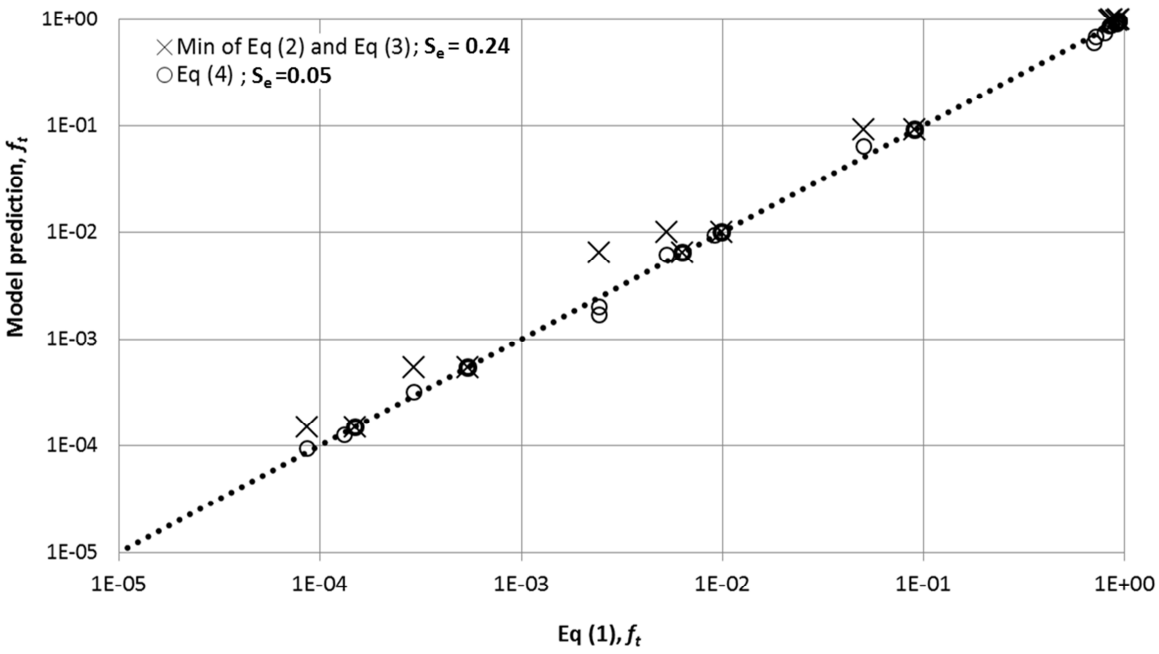
715 Yuan G, Peng H, Huang C, Hu J (2016) Ubiquitous Occurrence of Fluorotelomer Alcohols in Eco-Friendly Paper-
716 Made Food-Contact Materials and Their Implication for Human Exposure. Environ Sci Technol 50:942–
717 950. doi: 10.1021/acs.est.5b03806

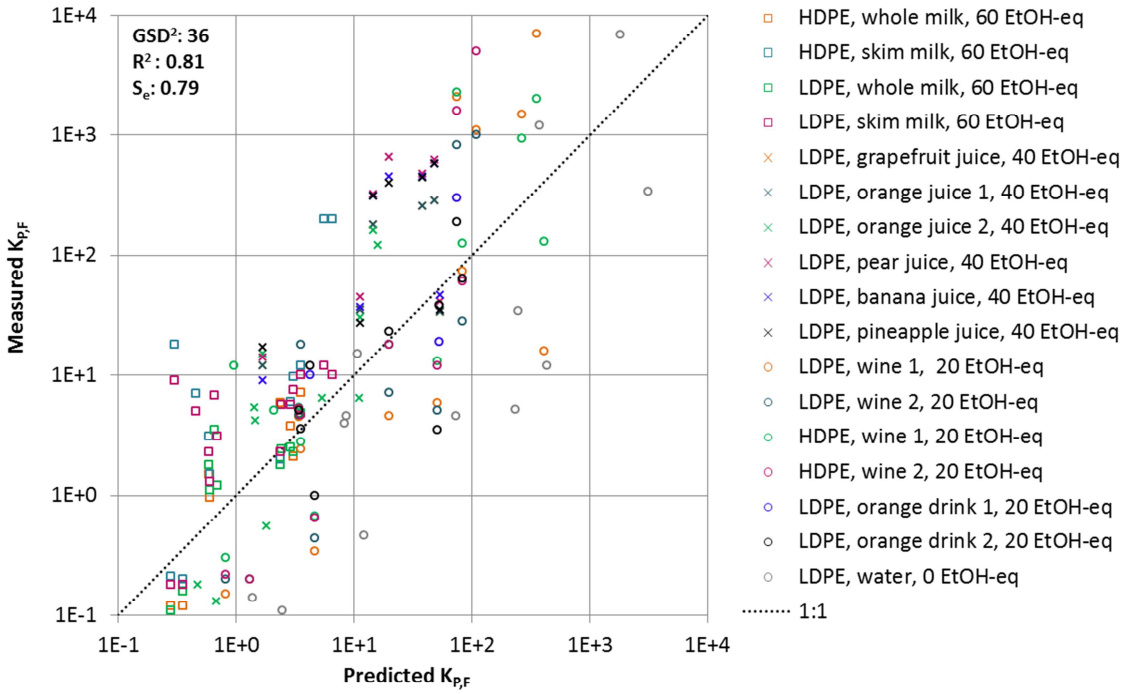
718

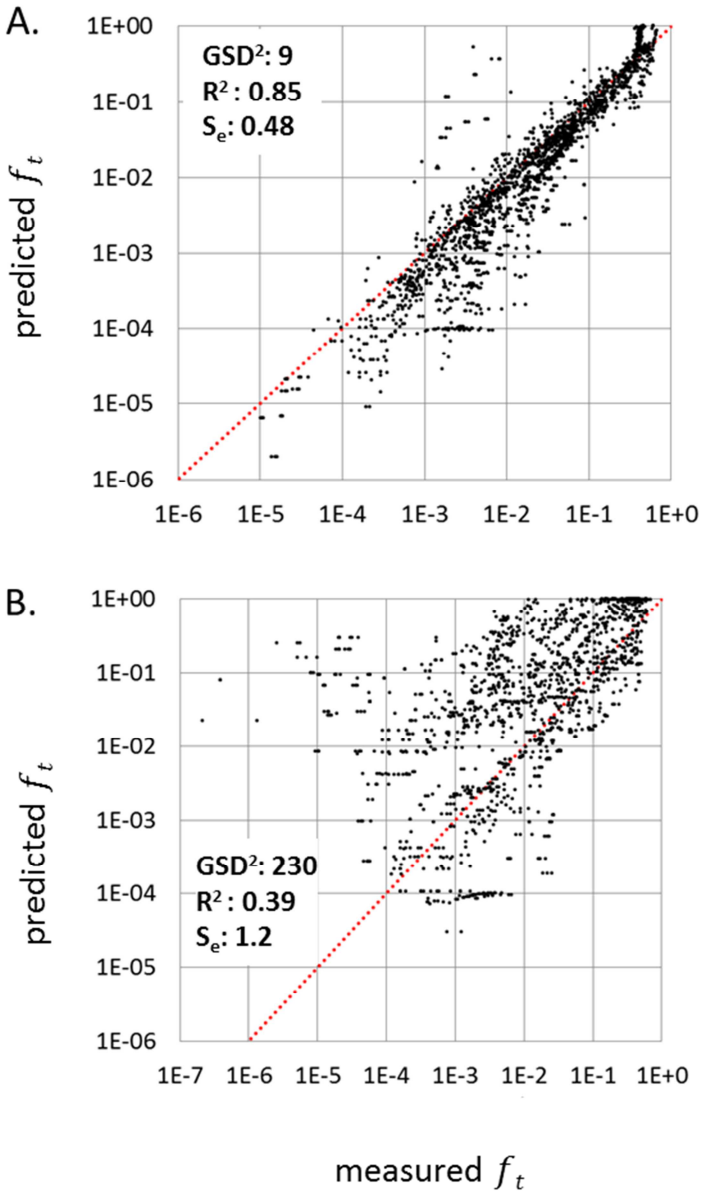
719




α = 1 × 10^3
α = 1
α = 1 × 10^−2
f_t
R²=0.99
R²=0.98
R²=0.97
R²=1
R²=0.98
R²=0.97
R²=1
R²=1
R²=1
time (s)
d_P²/D_P = 2.7 h
≈ 3m
d_P²/D_P = 317 y
≈ 10 y
d_P²/D_P = 3.17 My
≈ 30 y







Highlights

- A rapid and accurate migration model for chemicals in food packaging was developed for exposure screening and assessment.
- The model estimates the product intake fraction due to transfer of organic chemicals in polymeric packaging to food.
- The model is a function of packaging, food, and chemical aspects, as well as time and temperature.
- The model performs well when compared to empirical data, but the diffusion coefficient estimation leads to uncertainty.
- The model is available for dissemination in a spreadsheet to facilitate application in prioritization and screening tools.